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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

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In re United S	States Patent Application of:)	
Applicant:	Ekwuribe et al.)	TECH CENTER 1600/2900
Serial No.:	09/429,798) Examiner:	Not Yet Assigned
Date Filed:	October 29, 1999) Group Art Unit:	Not Yet Assigned
Title:	Blood-Brain Barrier Therapeutics)) _)	RECEIVED
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FIRST CLASS MAILING CERTIFICATE

Group 3700

I hereby certify that this paper is being deposited this date with the U.S. Postal Service as First Class Mail in an envelope addressed to the Assistant Commissioner for Patents, Washington, DC 20231, under the provisions of 37 CFR 1.8.

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INFORMATION DISCLOSURE STATEMENT

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Assistant Commissioner for Patents Washington, D.C. 20231

Sir:

Pursuant to 37 C.F.R. §1.56, the attention of the Patent and Trademark Office is hereby directed to the reference(s) listed on the attached PTO-1449. One copy of each reference is attached. It is respectfully requested that the information be expressly considered during the prosecution of this application, and that the reference(s) be made of record therein and appear among the "References Cited" on any patent to issue therefrom.

- I. This Information Disclosure Statement is being filed within three months of the U.S. filing date OR before the mailing date of a first Office Action on the merits. No certification or fee is required.
- 2. This Information Disclosure Statement is being filed more than three months after the U.S. filing date AND after the mailing date of the first Office Action on the merits, but before the mailing date of a Final Rejection or Notice of Allowance.

,	☐ a.	I hereby certify that each item of information contained in this Information Disclosure Statement was cited in a communication from the U.S. International Searching Atthough Item 1600/2900 counterpart international application not more than three months prior to the filing of this Information Disclosure Statement. 37 C.F.R. §1.97(e)(1).
•	□ b.	I hereby certify that no item of information in this Information Disclosure Statement was cited in a communication from a foreign patent office in a counterpart foreign application or, to my knowledge after making reasonable inquiry, was known to any individual designated in 37 CFR §1.56(c) more than three months prior to the filing of this Information Disclosure Statement. 37 C.F.R. §1.97(e)(2).
	c.	Attached is our check no in the amount of \$ in payment of the fee under 37 C.F.R. §1.17(p). Please credit or debit Deposit Account No as needed to ensure consideration of the disclosed information. Two duplicate copies of this paper are attached.
☐ 3.	and after Issue F Attacher C.F.R.	formation Disclosure Statement is being filed more than three months after the U.S. filing date er the mailing date of a Final Rejection or Notice of Allowance, but before payment of the ee. Applicant(s) hereby petition(s) that the Information Disclosure Statement be considered. ed is our check no in the amount of \$130.00 in payment of the petition fee under 37 §1.17(i)(1). Please credit or debit Deposit Account No as needed to ensure eration of the disclosed information. Two duplicate copies of this paper are attached.
	a.	I hereby certify that each item of information contained in this Information Disclosure Statement was cited in a communication from a foreign patent office in a counterpart foreign application not more than three months prior to the filing of this Information Disclosure Statement. 37 C.F.R. §1.97(e)(1).
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Respectfully submitted,

William A. Barrett

Registration No. 42,296

INTELLECTUAL PROPERTY/ TECHNOLOGY LAW

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Attorney Ref: 4012-113 DIV 1

Group 3700

FORM PTO-1449 US Dept. of Commerce Patent and Trademark Office			ATTORNEY DOCKET NO. SERIAL NOMAY 2000 09/429,798			2000		
• Patent and Trademark Office		4012-113 DIV1		TECH CENTER 1600/2				
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EXAMINER INITIAL		PATENT NUMBER	ISSUE DATE	NAME	CLASS	SUBCLASS	IF APPRO	
	AZ	5,559,213	24 Sep 1996	Hakimi et al.				
	BA	5,747,646	5 May 1998	Hakimi et al.				
	BB	5,286,637	15 Feb. 1994	Veronese et al.				
	BC	5,631,263	20 May 1997	Portoghese et al.				
	BD	5,602,099	11 Feb. 1997	Schiller				
	BE	5,545,719	13 Aug. 1996	Shashoua et al.				
	BF	5,641,861	24 Jun. 1997	Dooley et al.				
	BG	5,663,295	2 Sep. 1997	Moreau et al.				
	ВН	5,786,447	28 Jul. 1998	Schiller et al.				
	BI	4,939,174	3 Jul. 1990	Shashoua				
	BJ	5,932,462	Aug. 3, 1999	Harris et al.				
	- L		FOREIG	ON PATENT DOCUMENTS				
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INFORMATION DI	SCLOSORE STATEMENT	Ekwuribe et al.			
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TPE		October 29, 1999			
DET. 0 6 1999 BR	Metabolism," Amer. Chem. Soc	ckaging. Peptide Delivery to the Central ., 1995: 317-337.			
B/BS	Pharmaceutical Preparations," F	pility of Insulin. 1. Hydrolytic Degradation Pharm. Res., 1992, 9 (6): 715-726.			
8 TRADENTE BT	Products During Storage of Pha	pility of Insulin. 2. Formation of Higher M rmaceutical Preparations," Pharm. Res., 1	992, 9 (6): 727-734.		
BU	Estradiol Chemical Delivery Sy	f Molecular Manipulation on the Estroger stem," J. Med. Chem., 1994, 37: 4237-42	44		
BV	Brewster, M.E., et al., "Efficacy Estradiol Brain Targeting," J. P	of a 3-Substituted Versus 17-Substiturted harm. Sci., 1994: A-E.	l Chemical Delivery System for		
BW	Brewster, M., et al., "Tissue Disthe Rat," J. Pharm. Studies," 19	stribution of LY231617, an Antioxidant w 95, 84 (7): 791-793.			
BX	Conradi, R.A., et al., "The Influ	ence of Peptide Structure on Transport Ac			
BY	Chen, C., et al., "Extensive Bilia Pharm. Res. J., 14: 345-350.	ary Excretion of the Model Opioid Peptid			
BZ	Chiou, G.C.Y., et al., "Systemic 509-514.	Delivery of Enkephalin Peptide through			
CA	Chun., W., et al., "Transmucosa	ll Delivery of Methionine Enkephalin. I: S Mucosa Extracts," J. Pharm.Sci., 1993, 82	olution Stability and Kinetics of (4): 373-378.		
СВ	Fix, J.A., "Oral Controlled Rele 1996, 13 (12): 1760-1763.	ase Technology for Peptides: Status and I	Future Prospects," Pharm. Res.,		
CC	Gibson, A.M., et al., "Specificit and Dynorphin-Related Peptide	y of Action of Human Brain Alanyl Amin s," Neuropeptides, 1989, 13: 259-262.	opeptidase on Leu-Enkephalin		
CD	Gish, D. T. et al., "Nucleic Acid	ds. 11. Synthesis of 5'-Esters of 1-β-D-Ar- ressive Activity," J. Med. Chem., 1971, 14	abinofuranosylcytosine Possessing 4(12): 1159-1162.		
CE	Hong, C. I. et al., "Nucleoside C	Conjugates. 7. Synthesis and Antitumor Augates of Ether Lipids," J. Med. Chem., 19	ctivity of 1-β-D- 986, 29: 2038-2044.		
CF	Horvat, J., et al., "Synthesis and	l Biological Activity of [Leu ³] Enkephalin s., 1988, 31: 499-507.	Derivatives Containing D-		
CG	Hostetler, K. Y. et al., "Synthes	is and Antiretroviral Activity of Phosphol s," The Journal of Biological Chemistry,	ipid Analogs of Azidothymidine 1990, 265(11): 6112-6117.		
СН	Kroll, R.A., et al., "Outwitting to Other Means," 1998 Neurosurg	he Blood-Brain Barrier for Therapeutic P	urposes: Osmotic Opening and		
CI	Maislos, M. et al., "The Source Therapeutic Insulin," J. Clin. In	of the Circulating Aggregate of Insulin in	Type I Diabetic Patients is		
CJ	Mosnaim, A.D., et al., "Studies Gen. Pharmac., 1988, 19 (5): 72	of the in Vitro Human Plasma Degradation	on of Methionine-Enkephalin,"		
СК	Nestor, J., "Improved Duration	of Action of Peptide Drugs," Amer. Chen	n Soc. 1995: 449-471.		
CL		inal Absorption of a Hydrophobic Polymon," Pharm. Res., 1990, 7 (8): 852-855.	er-Conjugated Protein Drug,		
	omanos, in an ony romanation	Continue on Page 4			
Examiner		DATEC	CONSIDERED		
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NFORMATION DISCLOSURE STATEMENT (use several sheets if necessary) OTHER DOCUMENTS (Including Author, Title, Journal-Date, Page Number, Etc.) FILING DATE Crober 29, 1999 OTHER DOCUMENTS (Including Author, Title, Journal-Date, Page Number, Etc.) FILING DATE Crober 29, 1999 OTHER DOCUMENTS (Including Author, Title, Journal-Date, Page Number, Etc.) Chen Soc. 1995; 265-296 Chen Soc. 1995; 265-299 Centrology, 1994; 239-245. CO Pardridge, W.M., "New Approaches to Drug Delivery of Blood-Brain Barrier Transport," J. Neurochem, 1998, 70 (5): 1781-1792. CO Pardridge, W.M., "New Approaches to Drug Delivery Through the Blood-Brain Barrier," Trends in Biotechnology, 1994; 239-245. CP Prokal-Tatra, K., et al., "Farsian-Targeted Delivery of a Leucine-Enkephalin Analogue by Retrometabolic Design," J. Med. Chem 39 (24). CQ Ratner, R. et al., "Farsian-Cargeted Delivery of a Leucine-Enkephalin Analogue by Retrometabolic Design," J. Med. Chem 39 (24). CR Robbins, D. C. et al., "Antibodies to Covalent Aggregates of Insulin in Blood of Insulin-Using Diabetic Patients," Diabetes, 1990, 39: 728-733. CR Robbins, D. C. et al., "Antibodies to Covalent Aggregates of Insulin in Blood of Insulin-Using Diabetic Patients," Diabetes, 1987, 36: 838-841. CS Saffran, M. et al., "A New Approach to the Oral Administration of Insulin and Other Peptide Drugs," Science, 1986, 23: 1081-1084. CT Sakaeda, T., et al., "Conjugation with L-Glutamic Acid for Brain Drug Delivery," Proceed. Intern. Symp. Control. Rel. Bioact. Mater., 1966, 23: 607-608. CU Shashoua, V.E., et al., "N-Aminoburyric Acid Esters. I. Symthesis, Brain Uptake, and Pharmacological Studies of Aliphatic and Steroid Esters of "Aminoburyric Acid Esters. I. Symthesis, Brain Uptake, and Pharmacological Studies of Aliphatic and Steroid Esters of "Aminoburyric Acid," J. Med. Chem., 1984, 27 (5): 660-664. CN Shashoua, V.E., et al., "N-Docosahexaenov), 3 Hydroxytyramine: A Depaninergic Compound that Pentrates the Blood-Brain Barrier and Suppresses Appetite," Life Sciences, 38 (1			•			
APPLICANT GROUP	FORM PTO-	1449		ATTORNEY DOCKET NO.	SERIAL NO. 09/429,798	
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(use several sheets if necessary) FILING DATE October 29, 1999 OTHER DOCUMENTS (Including Author, Title, Journal-Date, Page Number, Etc.) OTHER DOCUMENTS (Including Author, Title, Journal-Date, Page Number, Etc.) CM Pardridge, W.M., "Blood-Brain Barrier Peptide Transport and Peptide Drug Delivery to the Brain," Amer. Chem Soc. 1995: 265-296. CN Pardridge, W.M., "CNS Drug Design Based on Principles of Blood-Brain Barrier Transport," J. Neurochem., 1998, 70 (5): 1781-1792. CO Pardridge, W.M., "New Approaches to Drug Delivery Through the Blood-Brain Barrier," Trends in Biotechnology, 1994: 239-245. CP Prokai-Tatrai, K., et al., "Brain-Targeted Delivery of a Leucine-Enkephalin Analogue by Retrometabolic Design," J. Med. Chem 99 (24). CQ Ratner, R. E. et al., "Persistent Curaneous Insulin Allergy Resulting from High-Molecular Weight Insulin Aggregates," Diabetes, 1990, 39 728-733. CR Robbins, D. C. et al., "Arthibodies to Covalent Aggregates of Insulin in Blood of Insulin-Using Diabetic Patients," Diabetes, 1987, 36: 838-841. CS Saffran, M. et al., "An Waw Approach to the Oral Administration of Insulin and Other Peptide Drugs," Science, 1986, 233: 1081-1084. CT Sakaeda, T., et al., "Conjugation with L-Glutamic Acid for Brain Drug Delivery," Proceed. Intern. Symp. Control. Ret. Bloact. Mater., 1966, 23: 607-608. CU Shashoua V.E., et al., "Y-Aminobutyric Acid Esters. I. Synthesis, Brain Uptake, and Pharmacological Studies of Aliphatic and Steroid Esters of y-Aminobutyric Acid," J. Med. Chem., 1984, 27 (5): 660-664. CV Shashoua, V.E., et al., "N-Doccoshexaenoyl, 3 Hydroxytyramine: A Dopaminergic Compound that Penetrates the Blood-Brain Barrier and Suppresses Appetite," Life Sciences, 58 (16): 1347-1354. CW Sim, L., et al., "In vitro Autoradiography of Receptor-Activated G Proteins in Rat Brain by Agonist-stimulated Guanylyl 5"-{If/"Shihol-Triphosphate Binding," Proc. Natl. Acad. Sci., USA, 1995, 92: 7242-7246. CX Terasaki, T., et al., "Oligopeptide Drug Delivery to the Brain," Amer. Chem. Soc. 1995: 29	î.					
October 29, 1999 OTHER DOCUMENTS (Including Author, Title, Journal-Date, Page Number, Etc.) OTHER DOCUMENTS (Including Author, Title, Journal-Date, Page Number, Etc.) CM Pardridge, W.M., "Blood-Brain Barrier Peptide Transport and Peptide Drug Delivery to the Brain," Amer. Chem Soc. 1995: 265-296. CN Pardridge, W.M., "Nos Drug Design Based on Principles of Blood-Brain Barrier Transport," J. Neurochem., 1998, 70 (5): 1781-1792. CO Pardridge, W.M., "New Approaches to Drug Delivery Through the Blood-Brain Barrier," Trends in Biotechnology, 1994: 239-245. CP Prokal-Tarral, K., et al., "Brain-Targeted Delivery of a Leucine-Enkephalin Analogue by Retrometabolic Design," J. Med. Chem 39 (24). CR Ratner, R. E. et al., "Persistent Cutaneous Insulin Allergy Resulting from High-Molecular Weight Insulin Aggregates," Diabetes, 1990, 39: 728-733. CR Robbins, D. C. et al., "Antibodies to Covalent Aggregates of Insulin in Blood of Insulin-Using Diabetic Patients," Diabetes, 1987, 36: 838-841. CS Saffran, M. et al., "A New Approach to the Oral Administration of Insulin and Other Peptide Drugs," Science, 1986, 23: 1081-1084. CT Sakaeda, T., et al., "Conjugation with L-Glutamic Acid for Brain Drug Delivery," Proceed. Intern. Symp. Control. Rel. Bioact. Mater., 1966, 23: 607-608. CU Shashoua V.E., et al., "Y-Aminobutyric Acid Esters. I. Synthesis, Brain Uptake, and Pharmacological Studies of Aliphatic and Steroid Esters of y-Aminobutyric Acid," J. Med. Chem., 1984, 27 (5): 660-664. CV Shashoua, V.E., et al., "N-Docosahexaenoy), 3 Hydroxytyramine. A Dopaminergic Amopund that Penetrates the Blood-Brain Barrier and Suppresses Appetite," Life Sciences, 58 (16): 1347-1354. CW Sim, L., et al., "In vitro Autoradiography of Receptor-Activated G Proteins in Rat Brain by Agonist stimulated Guanyly! 5"-(7!3"S)thio]-Triphosphate Binding," Proc. Natl. Acad. Sci., USA, 1995, 92: 7242-7246. CX Teraski, T., et al., "Babid Communication. Adamantane as a Brain-Directed Drug Carrier for Poorly Absorbed Drug: Antinociceptive Effects of [INFORMAT	ION DI	SCLOSURE STATEMENT			
October 29, 1999 OTHER DOCUMENTS (Including Author, Title, Journal-Date, Page Number, Etc.) OTHER DOCUMENTS (Including Author, Title, Journal-Date, Page Number, Etc.) CM Pardridge, W.M., "Blood-Brain Barrier Peptide Transport and Peptide Drug Delivery to the Brain," Amer. Chem Soc. 1995: 265-296. CN Pardridge, W.M., "CNS Drug Design Based on Principles of Blood-Brain Barrier Transport," J. Neurochem. 1998, 70 (5): 1781-1792. CO Pardridge, W.M., "New Approaches to Drug Delivery Through the Blood-Brain Barrier," Trends in Biotechnology, 1994: 239-245. CP Prokai-Tatral, K., et al., "Brain-Targeted Delivery of a Leucine-Enkephalin Analogue by Retrometabolic Design," J. Med. Chem 39 (24). CQ Ratner, R. E. et al., "Persistent Cutaneous Insulin Allergy Resulting from High-Molecular Weight Insulin Aggregates," Diabetes, 1990, 39:. 728-733. CR Robbins, D. C. et al., "Antibodies to Covalent Aggregates of Insulin in Blood of Insulin-Using Diabetic Patients," Diabetes, 1987, 36: 838-841. CS Saffran, M. et al., "A New Approach to the Oral Administration of Insulin and Other Peptide Drugs," Science, 1986, 233: 1081-1084. CT Sakaeda, T., et al., "Conjugation with L-Glutamic Acid for Brain Drug Delivery," Proceed. Intern. Symp. Control. Rel. Bioact. Mater., 1966, 23: 607-608. CU Shashoua, V.E., et al., "Y-Aminobutyric Acid Esters. I. Synthesis, Brain Uptake, and Pharmacological Studies of Aliphatic and Steroid Esters of y-Aminobutyric Acid," J. Med. Chem., 1984, 27 (5): 660-664. CV Shashoua, V.E., et al., "N-Docosahevaenoyl, 3 Hydroxytyramine. A Dopaminergic propound that Penetrates the Blood-Brain Barrier and Suppresses Appetite," Life Sciences, 58 (16): 1347-1354. CW Sim, L., et al., "In vitro Autoradiography of Receptor-Activated G Proteins in Rat Brain by Agonist-stimulated Guanylyl 5"-[y12"S]thio]-Triphosphate Binding," Proc. Natl. Acad. Sci., USA, 1995, 92: 7242-7246. CX Teraski, T., et al., "Babid Communication. Adamantane as a Brain-Directed Drug Carrier for Poorly Absorbed Drug: Antinociceptive Effects o	(m	se sever	al sheets if necessary)	FILING DATE	GROUP	
OTHER DOCUMENTS (Including Author, Title, Journal-Date, Page Number, Etc.) Pardridge, W.M., "Blood-Brain Barrier Peptide Transport and Peptide Drug Delivery to the Brain," Amer. Chem Soc. 1995; 265-296. CN Pardridge, W.M., "CNS Drug Design Based on Principles of Blood-Brain Barrier Transport," J. Neurochem., 1998, 70 (5): 1781-1792. CN Pardridge, W.M., "Wew Approaches to Drug Delivery Through the Blood-Brain Barrier," Trends in Biotechnology, 1994: 239-245. CP Prokai-Tarra, K., et al., "Brain-Targeted Delivery of a Leucine-Enkephalin Analogue by Retrometabolic Design," J. Med. Chem 39 (24). CQ Ratner, R. E. et al., "Persistent Cutaneous Insulin Allergy Resulting from High-Molecular Weight Insulin Aggregates," Diabetes, 1990, 39: 728-733. CR Robbins, D. C. et al., "Antibodies to Covalent Aggregates of Insulin in Blood of Insulin-Using Diabetic Patients," Diabetes, 1987, 36: 838-841. CS Saffran, M. et al., "A New Approach to the Oral Administration of Insulin and Other Peptide Drugs," Science, 1986, 233: 1081-1084. CS Sakeda, T., et al., "Conjugation with L-Glutamic Acid for Brain Drug Delivery," Proceed. Intern. Symp. Control. Rel. Bioact. Mater., 1966, 23: 607-608. CU Shashoua V.E., et al., "Y-Aminobutyric Acid Esters. I. Synthesis, Brain Uptake, and Pharmacological Studies of Aliphatic and Steroid Esters of y-Aminobutyric Acid," J. Med. Chem., 1984, 27 (5): 660-664. CV Shashoua, V.E., et al., "N-Docosahexaenoyl, 3 Hydroxytyramine: A Dopaminergic Compound that Penetrates the Blood-Brain Barrier and Suppresses Appetite," Life Sciences, 38 (16): 1347-1354. CW Sim, L., et al., "Indoor Autoradiography of Receptor-Activated Of Proteins in Rat Brain by Agonist-stimulated Guanylyl 5'-[7] ²⁸ S[thio]-Triphosphate Binding," Proc. Natl. Acad. Sci., USA, 1995, 92: 7242-7246. CY Tarsaki, T., et al., "Robid Communication. Adamantane as a Brain-Directed Drug Carrier for Poorly Absorbed Drug: Antinociceptive Effects of [D-Ala*] Leu-Enkephalin Derivatives Conjugated with the 1-Adamantane Moiety," Biochemical Pharmac		30 701	ar sheets it necessary,			
OTHER DOCUMENTS (Including Author, Title, Journal-Date, Page Number, Etc.) OTHER DOCUMENTS (Including Author, Title, Journal-Date, Page Number, Etc.) Pardridge, W.M., "Blood-Brain Barrier Peptide Transport and Peptide Drug Delivery to the Brain," Amer. Chem Soc. 1995; 265-296. CN Pardridge, W.M., "Nox Drug Design Based on Principles of Blood-Brain Barrier Transport," J. Neurochem., 1998, 70 (5): 1781-1792. CO Pardridge, W.M., "Nox Drug Design Based on Principles of Blood-Brain Barrier Transport," J. Neurochem., 1998, 70 (5): 1781-1792. CO Pardridge, W.M., "New Approaches to Drug Delivery Through the Blood-Brain Barrier," Trends in Biotechnology, 1994: 239-245. CP Prokai-Tarrai, K., et al., "Brain-Targeted Delivery of a Leucine-Enkephalin Analogue by Retrometabolic Design," J. Med. Chem 39 (24). CQ Ratner, R. E. et al., "Persistent Cutaneous Insulin Allergy Resulting from High-Molecular Weight Insulin Aggregates," Diabetes, 1990, 93: 728-733. CR Robbins, D. C. et al., "Antibodies to Covalent Aggregates of Insulin in Blood of Insulin-Using Diabetic Patients," Diabetes, 1997, 36: 838-841. CS Saffran, M. et al., "A New Approach to the Oral Administration of Insulin and Other Peptide Drugs," Science, 1986, 233: 1081-1084. CS Saffran, M. et al., "Conjugation with L-Glutamic Acid for Brain Drug Delivery," Proceed. Intern. Symp. Control. Rel. Bioact. Mater., 1966, 23: 607-608. CU Shashoua V.E., et al., ""T-Aminobutyric Acid Esters. I. Synthesis, Brain Uptake, and Pharmacological Studies of Aliphatic and Steroid Esters of y-Aminobutyric Acid," J. Med. Chem., 1984, 27 (5): 660-664. CV Shashoua, V.E., et al., ""D-Docosahexenov), 3 Hydroxytyramine: A Dopaminergic Compound that Penetrates the Blood-Brain Barrier and Suppresses Appetite," Life Sciences, 58 (16): 1347-1354. CW Sim, L., et al., "In vitro Autoradiography of Receptor-Activated G Proteins in Rat Brain by Agonist-stimulated Guanylyl 5'-[q'18]thio]-Triphosphate Binding," Proc. Natl. Acad. Sci., USA, 1995, 92: 7242-7246. CX Terasaki, T., et al., "Suppr	PE			,		
CM Pardridge, W.M., "Blood-Brain Barrier Peptide Transport and Peptide Drug Delivery to the Brain," Amer. Chem Soc. 1995; 265-296. CN Pardridge, W.M., "CNS Drug Design Based on Principles of Blood-Brain Barrier Transport," J. Neurochem., 1998, 70 (5): 1781-1792. CO Pardridge, W.M., "New Approaches to Drug Delivery Through the Blood-Brain Barrier," Trends in Biotechnology, 1994: 239-245. CP Prokai-Tatrai, K., et al., "Brain-Targeted Delivery of a Leucine-Enkephalin Analogue by Retrometabolic Design," J. Med. Chem 39 (24). CQ Ratner, R. E. et al., "Persistent Cutaneous Insulin Allergy Resulting from High-Molecular Weight Insulin Aggregates," Diabetes, 1990, 39: 728-733. CR Robbins, D. C. et al., "Antibodies to Covalent Aggregates of Insulin in Blood of Insulin-Using Diabetic Patients," Diabetes, 1987, 36: 838-841. CS Saffran, M. et al., "A New Approach to the Oral Administration of Insulin and Other Peptide Drugs," Science, 1986, 233: 1081-1084. CT Sakaeda, T., et al., "Conjugation with L-Glutamic Acid for Brain Drug Delivery," Proceed. Intern. Symp. Control. Rel. Bioact. Mater., 1966, 23: 607-608. CU Shashoua, V.E., et al., "Y-Aminobutyric Acid Esters. I. Synthesis, Brain Uptake, and Pharmacological Studies of Aliphatic and Steroid Esters of y-Aminobutyric Acid," J. Med. Chem., 1984, 27 (5): 660-664. CV Shashoua, V.E., et al., "N-Docosahexaenoyl, 3 Hydroxytyramine: A Dopaminergic Compound that Penetrates the Blood-Brain Barrier and Suppresses Appetite," Life Sciences, 58 (16): 1347-1354. CW Sim, L., et al., "In vitro Autoradiography of Receptor-Activated G Proteins in Rat Brain by Agonist-stimulated Guanylyl 5¹-{y 3*S thio}-Triphosphate Binding," Proc. Natl. Acad. Sci., USA, 1995, 92: 7242-7246. CX Terasaki, T., et al., "Nebid Communication. Adamantane as a Brain-Directed Drug Carrier for Poorly Absorbed Drug: Antinociceptive Effects of [D-Ala*] Leu-Enkephalin Derivatives Conjugated with the 1-Adamantane Moiety," Biochemical Pharmacology, 1991, 41 (4): R5-R8. Wagner, J., et al., "Neuropharmacology of	<u> </u>					
CM Pardridge, W.M., "Blood-Brain Barrier Peptide Transport and Peptide Drug Delivery to the Brain," Amer. Chem Soc. 1995: 265-296. CN Pardridge, W.M., "CNS Drug Design Based on Principles of Blood-Brain Barrier Transport," J. Neurochem., 1998, 70 (5): 1781-1792. CO Pardridge, W.M., "New Approaches to Drug Delivery Through the Blood-Brain Barrier," Trends in Biotechnology, 1994: 239-245. CP Prokai-Tatrai, K., et al., "Brain-Targeted Delivery of a Leucine-Enkephalin Analogue by Retrometabolic Design," J. Med. Chem 39 (24). CQ Ratner, R. E. et al., "Persistent Cutaneous Insulin Allergy Resulting from High-Molecular Weight Insulin Aggregates," Diabetes, 1990, 39: 728-733. CR Robbins, D. C. et al., "Antibodies to Covalent Aggregates of Insulin in Blood of Insulin-Using Diabetic Patients," Diabetes, 1987, 36: 838-841. CS Saffran, M. et al., "A New Approach to the Oral Administration of Insulin and Other Peptide Drugs," Science, 1986, 233: 1081-1084. CT Sakaeda, T., et al., "Conjugation with L-Glutamic Acid for Brain Drug Delivery," Proceed. Intern. Symp. Control. Rel. Bioact. Mater., 1966, 23: 607-608. CU Shashoua V.E., et al., "Y-Aminobutyric Acid Esters. I. Synthesis, Brain Uptake, and Pharmacological Studies of Aliphatic and Steroid Esters of y-Aminobutyric Acid," J. Med. Chem., 1984, 27 (5): 660-664. CV Shashoua, V.E., et al., "N-Docosahexaenoyl, 3 Hydroxytyramine: A Dopaminergic Compound that Penetrates the Blood-Brain Barrier and Suppresses Appetite," Life Sciences, 58 (16): 1347-1354. CW Sim, L., et al., "In vitro Autoradiography of Receptor-Activated G Proteins in Rat Brain by Agonist-stimulated Guanylyl 5'-[y] ¹⁵ S[htio]-Triphosphate Binding," Proc. Natl. Acad. Sci., USA, 1995, 92: 7242-7246. CX Terasaki, T., et al., "Gligopeptide Drug Delivery to the Brain," Amer. Chem. Soc. 1995: 297-316. CY Tsuzuki, N., et al., "Rabid Communication. Adamantane as a Brain-Directed Drug Carrier for Poorly Absorbed Drug: Antinociceptive Effects of [D-Ala*] Leu-Enkephalin Derivatives Conjugated with the I-Adamanta	n s 1009		OTHER DOCUMENTS (Includ	ing Author, Title, Journal-Date, Pag	e Number, Etc.)	
CN Pardridge, W.M., "CNS Drug Design Based on Principles of Blood-Brain Barrier Transport," J. Neurochem., 1998, 70 (5): 1781-1792. CO Pardridge, W.M., "New Approaches to Drug Delivery Through the Blood-Brain Barrier," Trends in Biotechnology, 1994: 239-245. CP Prokai-Tatrai, K., et al., "Brain-Targeted Delivery of a Leucine-Enkephalin Analogue by Retrometabolic Design," J. Med. Chem 39 (24). CQ Ratner, R. E. et al., "Persistent Cutaneous Insulin Allergy Resulting from High-Molecular Weight Insulin Aggregates," Diabetes, 1990, 39:. 728-733. CR Robbins, D. C. et al., "Antibodies to Covalent Aggregates of Insulin in Blood of Insulin-Using Diabetic Patients," Diabetes, 1987, 36: 838-841. CS Saffran, M. et al., "A New Approach to the Oral Administration of Insulin and Other Peptide Drugs," Science, 1986, 233: 1081-1084. CT Sakaeda, T., et al., "Conjugation with L-Glutamic Acid for Brain Drug Delivery," Proceed. Intern. Symp. Control. Rel. Bioact. Mater., 1966, 23: 607-608. CU Shashoua V.E., et al., "Y-Aminobutyric Acid Esters. I. Synthesis, Brain Uptake, and Pharmacological Studies of Aliphatic and Steroid Esters of y-Aminobutyric Acid," J. Med. Chem., 1984, 27 (5): 660-664. CV Shashoua, V.E., et al., "N-Doosabexaenoyl, 3 Hydroxytyramine: A Dopaminergic Compound that Penetrates the Blood-Brain Barrier and Suppresses Appetite," Life Sciences, 58 (16): 1347-1354. CW Sim, L., et al., "In vitro Autoradiography of Receptor-Activated G Proteins in Rat Brain by Agoniststimulated Guanylyl 5":[y ⁷⁵ S thio]-Triphosphate Binding," Proc. Natl. Acad. Sci., USA, 1995, 92: 7242-7246. CX Terasaki, T., et al., "Oligopeptide Drug Delivery to the Brain," Amer. Chem. Soc. 1995: 297-316. CY Tsuzuki, N., et al., "Rabid Communication. Adamantane as a Brain-Directed Drug Carrier for Poorly Absorbed Drug: Antinociceptive Effects of [D-Ala*] Leu-Enkephalin Derivatives Conjugated with the 1-Adamantane Moiety," Biochemical Pharmacology, 1991, 41 (4): RS-R8. CZ Wagner, J., et al., "Neuropharmacology of Endogenous Opiol Peptive," P) J.	CM		Barrier Peptide Transport and Peptide	Drug Delivery to the Brain," Amer.	
Neurochem., 1998, 70 (5): 1781-1792. CO Pardridge, W.M., "New Approaches to Drug Delivery Through the Blood-Brain Barrier," Trends in Biotechnology, 1994: 239-245. CP Prokai-Tatrai, K., et al., "Farsin-Targeted Delivery of a Leucine-Enkephalin Analogue by Retrometabolic Design," J. Med. Chem 39 (24). CQ Ratner, R. E. et al., "Persistent Cutaneous Insulin Allergy Resulting from High-Molecular Weight Insulin Aggregates," Diabetes, 1990, 39:. 728-733. CR Robbins, D. C. et al., "Antibodies to Covalent Aggregates of Insulin in Blood of Insulin-Using Diabetic Patients," Diabetes, 1987, 36: 838-841. CS Saffran, M. et al., "A New Approach to the Oral Administration of Insulin and Other Peptide Drugs," Science, 1986, 233: 1081-1084. CT Sakead, T., et al., "Conjugation with L-Glutamic Acid for Brain Drug Delivery," Proceed. Intern. Symp. Control. Rel. Bioact. Mater., 1966, 23: 607-608. CU Shashoua V.E., et al., "N-Aminobutyric Acid Esters. I. Synthesis, Brain Uptake, and Pharmacological Studies of Aliphatic and Steroid Esters of y-Aminobutyric Acid," J. Med. Chem., 1984, 27 (5): 660-664. CV Shashoua, V.E., et al., "N-Docosahexaenoyl, 3 Hydroxytyramine: A Dopaminergic Compound that Penetrates the Blood-Brain Barrier and Suppresses Appetite," Life Sciences, 58 (16): 1347-1354. CW Sim, L., et al., "In viro Autoradiography of Receptor-Activated G Proteins in Rat Brain by Agonist-stimulated Guanylyl 5'-[y[³⁵ S]thio]-Triphosphate Binding," Proc. Natl. Acad. Sci., USA, 1995, 92: 7242-7246. CX Terasaki, T., et al., "Gligopeptide Drug Delivery to the Brain," Amer. Chem. Soc. 1995: 297-316. CY Tsuzuki, N., et al., "Rabid Communication. Adamantane as a Brain-Directed Drug Carrier for Poorty Absorbed Drug: Antinociceptive Effects of [D-Ala ²] Leu-Enkephalin Derivatives Conjugated with the 1-Adamantane Moiety," Biochemical Pharmacology, 1991, 41 (4): R5-R8. CZ Wagner, J., et al., "Neuropharmacology of Endocenous Opioid Peptides," Psychopharmacology: The Fourth Generation of Progress, 1995: 519-529. DA Weber, S.J., et a						
CO Pardridge, W.M., "New Approaches to Drug Delivery Through the Blood-Brain Barrier," Trends in Biotechnology, 1994: 239-245. CP Prokai-Tatrai, K., et al., "Brain-Targeted Delivery of a Leucine-Enkephalin Analogue by Retrometabolic Design," J. Med. Chem 39 (24). CQ Ratner, R. E. et al., "Persistent Cutaneous Insulin Allergy Resulting from High-Molecular Weight Insulin Aggregates," Diabetes, 1990, 39. 728-733. CR Robbins, D. C. et al., "Antibodies to Covalent Aggregates of Insulin in Blood of Insulin-Using Diabetic Patients," Diabetes, 1987, 36: 838-841. CS Saffran, M. et al., "A New Approach to the Oral Administration of Insulin and Other Peptide Drugs," Science, 1986, 233: 1081-1084. CT Sakaeda, T., et al., "Conjugation with L-Glutamic Acid for Brain Drug Delivery," Proceed. Intern. Symp. Control. Rel. Bioact. Mater., 1966, 23: 607-608. CU Shashoua V.E., et al., "N-Mocosahexaenoyl, 3 Hydroxytyramine: A Dopaminergic Compound that Penetrates the Blood-Brain Barrier and Suppresses Appetite," Life Sciences, 58 (16): 1347-1354. CW Sim, L., et al., "In vitro Autoradiography of Receptor-Activated G Proteins in Rat Brain by Agonist-stimulated Guanylyl 5"- [γ[7 ¹⁸ S]thio]-Triphosphate Binding," Proc. Natl. Acad. Sci., USA, 1995, 92: 7242-7246. CX Terasaki, T., et al., "Rabid Communication. Adamantane as a Brain-Directed Drug Carrier for Poorly Absorbed Drug: Antinociceptive Effects of [D-Ala*] Leu-Enkephalin Derivatives Conjugated with the 1-Adamantane Moiety," Biochemical Pharmacology, 1991, 41 (4): 85-88. CZ Wagner, J., et al., "Disribution and Analgesia of [³ H][D-PEN ² , D-PEN ³] Enkephalin and Two Halogenated Analogs after Intravenous Administration," J. Pharm. Exper. Ther., 1991, 259: 1109-1112. DB Weber, S.J., et al., "Disribution and Analgesia of [³ H][D-PEN ² , D-PEN ³] Enkephalin after Intraperitoneal, Intravenous, Oral and Subcutaneous Administration," J. Pharm. Exper. Ther., 1992, 263: 1308-1316.	TRADEMAR	CN	Neurochem., 1998, 70 (5): 178	1-1792.		
Biotechnology, 1994: 239-245. CP Prokai-Tatrai, K., et al., "Brain-Targeted Delivery of a Leucine-Enkephalin Analogue by Retrometabolic Design," J. Med. Chem. 39 (24). CQ Ratner, R. E. et al., "Persistent Cutaneous Insulin Allergy Resulting from High-Molecular Weight Insulin Aggregates," Diabetes, 1990, 39:. 728-733. CR Robbins, D. C. et al., "Antibodies to Covalent Aggregates of Insulin in Blood of Insulin-Using Diabetic Patients," Diabetes, 1987, 36: 838-841. CS Saffran, M. et al., "A New Approach to the Oral Administration of Insulin and Other Peptide Drugs," Science, 1986, 23: 1081-1084. CT Sakaeda, T., et al., "Conjugation with L-Glutamic Acid for Brain Drug Delivery," Proceed. Intern. Symp. Control. Rel. Bioact. Mater., 1966, 23: 607-608. CU Shashoua V.E., et al., "Y-Aminobutyric Acid Esters. I. Synthesis, Brain Uptake, and Pharmacological Studies of Aliphatic and Steroid Esters of γ-Aminobutyric Acid," J. Med. Chem., 1984, 27 (5): 660-664. CV Shashoua, V.E., et al., "N-Docosahexaenoyl, 3 Hydroxytyramine: A Dopaminergic Compound that Penetrates the Blood-Brain Barrier and Suppresses Appetite," Life Science, 58 (16): 1347-1354. CW Sim, L., et al., "In vitro Autoradiography of Receptor-Activated G Proteins in Rat Brain by Agonist-stimulated Guanyly! 5'-{γ² S thio}-Triphosphate Binding," Proc. Natl. Acad. Sci., USA, 1995, 92: 7242-7246. CX Terasaki, T., et al., "Oligopeptide Drug Delivery to the Brain," Amer. Chem. Soc. 1995: 297-316. CY Tsuzuki, N., et al., "Rabid Communication. Adamantane as a Brain-Directed Drug Carrier for Poorly Absorbed Drug: Antinociceptive Effects of [D-Ala²] Leu-Enkephalin Derivatives Conjugated with the 1-Adamantane Moiety," Biochemical Pharmacology, 1991, 41 (4): RS-R8. CZ Wagner, J., et al., "Subiribution and Analgesia of [*H][D-PEN², D-PEN³] Enkephalin and Two Halogenated Analogs after Intravenous Administration," J. Pharm. Exper. Ther., 1991, 259: 1109-1112. DB Weber, S.J., et al., "Whole Body and Brain Distribution of [*H][Cyclic [D-PEN², D-PEN³] Enkephalin after		СО	Pardridge, W.M., "New Approa	aches to Drug Delivery Through the Blo	ood-Brain Barrier," Trends in	
Design," J. Med. Chem 39 (24). CQ Ratmer, R. E. et al., "Persistent Cutaneous Insulin Allergy Resulting from High-Molecular Weight Insulin Aggregates," Diabetes, 1990, 39:. 728-733. CR Robbins, D. C. et al., "Antibodies to Covalent Aggregates of Insulin in Blood of Insulin-Using Diabetic Patients," Diabetes, 1987, 36: 838-841. CS Saffran, M. et al., "A New Approach to the Oral Administration of Insulin and Other Peptide Drugs," Science, 1986, 233: 1081-1084. CT Sakaeda, T., et al., "Conjugation with L-Glutamic Acid for Brain Drug Delivery," Proceed. Intern. Symp. Control. Rel. Bioact. Mater., 1966, 23: 607-608. CU Shashoua V.E., et al., "Y-Aminobutyric Acid Esters. 1. Synthesis, Brain Uptake, and Pharmacological Studies of Aliphatic and Steroid Esters of y-Aminobutyric Acid." J. Med. Chem., 1984, 27 (5): 660-664. CV Shashoua, V.E., et al., "N-Docosahexaenoyl, 3 Hydroxytyramine: A Dopaminergic Compound that Penetrates the Blood-Brain Barrier and Suppresses Appetite," Life Sciences, 58 (16): 1347-1354. CW Sim, L., et al., "In vitro Autoradiography of Receptor-Activated G Proteins in Rat Brain by Agonist-stimulated Guanylyl 5'-[y[²⁸ S]thio]-Triphosphate Binding," Proc. Natl. Acad. Sci., USA, 1995, 92: 7242-7246. CX Terasaki, T., et al., "Gligopeptide Drug Delivery to the Brain," Amer. Chem. Soc. 1995: 297-316. CY Tsuzuki, N., et al., "Rabid Communication. Adamantane as a Brain-Directed Drug Carrier for Poorly Absorbed Drug: Antinociceptive Effects of [D-Ala*] Leu-Enkephalin Derivatives Conjugated with the 1-Adamantane Moiety," Biochemical Pharmacology, 1991, 41 (4): R5-R8. CZ Wagner, J., et al., "Neuropharmacology of Endogenous Opioid Peptides," Psychopharmacology: The Fourth Generation of Progress, 1995: 519-529. DA Weber, S.J., et al., "Distribution and Analgesia of [² H][D-PEN ² , D-PEN ²] Enkephalin and Two Halogenated Analogs after Intravenous Administration," J. Pharm. Exper. Ther., 1991, 259: 1109-1112. DB Weber, S.J., et al., "Whole Body and Brain Distribution of [² H]Cyclic [D-PEN ² , D-PE			Biotechnology, 1994: 239-245.			
CQ Ratner, R. E. et al., "Persistent Cutaneous Insulin Allergy Resulting from High-Molecular Weight Insulin Aggregates," Diabetes, 1990, 39:. 728-733. CR Robbins, D. C. et al., "Antibodies to Covalent Aggregates of Insulin in Blood of Insulin-Using Diabetic Patients," Diabetes, 1987, 36: 838-841. CS Saffran, M. et al., "A New Approach to the Oral Administration of Insulin and Other Peptide Drugs," Science, 1986, 233: 1081-1084. CT Sakaeda, T., et al., "Conjugation with L-Glutamic Acid for Brain Drug Delivery," Proceed. Intern. Symp. Control. Rel. Bioact. Mater., 1966, 23: 607-608. CU Shashoua V.E., et al., "γ-Aminobutyric Acid Esters. 1. Synthesis, Brain Uptake, and Pharmacological Studies of Aliphatic and Steroid Esters of γ-Aminobutyric Acid," J. Med. Chem., 1984, 27 (5): 660-664. CV Shashoua, V.E., et al., "N-Docosahexaenoyl, 3 Hydroxytyramine: A Dopaminergic Compound that Penetrates the Blood-Brain Barrier and Suppresses Appetite," Life Sciences, 58 (16): 1347-1354. CW Sim, L., et al., "in vitro Autoradiography of Receptor-Activated G Proteins in Rat Brain by Agonist-stimulated Guanylyl 5'-{γ ³⁵ S thio -Triphosphate Binding," Proc. Natl. Acad. Sci., USA, 1995, 92: 7242-7246. CX Terasaki, T., et al., "Oligopeptide Drug Delivery to the Brain," Amer. Chem. Soc. 1995: 297-316. CY Tsuzuki, N., et al., "Rabid Communication. Adamantane as a Brain-Directed Drug Carrier for Poorly Absorbed Drug: Antinociceptive Effects of [D-Ala*] Leu-Enkephalin Derivatives Conjugated with the 1-Adamantane Moiety," Biochemical Pharmacology, 1991, 41 (4): R5-R8. CZ Wagner, J., et al., "Neuropharmacology of Endogenous Opioid Peptides," Psychopharmacology: The Fourth Generation of Progress, 1995: 519-529. DA Weber, S.J., et al., "Distribution and Analgesia of [³H][D-PEN³, D-PEN³] Enkephalin and Two Halogenated Analogs after Intravenous Administration," J. Pharm. Exper. Ther., 1991, 259: 1109-1112. DB Weber, S.J., et al., "Whole Body and Brain Distribution of [³H]Cyclic [D-PEN³, D-PEN³] Enkephalin after Intraperitoneal, Int	-	CP	Prokai-Tatrai, K., et al., "Brain-	-Targeted Delivery of a Leucine-Enkep	halin Analogue by Retrometabolic	
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CR Robbins, D. C. et al., "Antibodies to Covalent Aggregates of Insulin in Blood of Insulin-Using Diabetic Patients," Diabetes, 1987, 36: 838-841. CS Saffran, M. et al., "A New Approach to the Oral Administration of Insulin and Other Peptide Drugs," Science, 1986, 233: 1081-1084. CT Sakaeda, T., et al., "Conjugation with L-Glutamic Acid for Brain Drug Delivery," Proceed. Intern. Symp. Control. Rel. Bioact. Mater., 1966, 23: 607-608. CU Shashoua V.E., et al., "Y-Aminobutyric Acid Esters. 1. Synthesis, Brain Uptake, and Pharmacological Studies of Aliphatic and Steroid Esters of γ-Aminobutyric Acid," J. Med. Chem., 1984, 27 (3): 660-664. CV Shashoua, V.E., et al., "N-Docosahexaenoyl, 3 Hydroxytyramine: A Dopaminergic Compound that Penetrates the Blood-Brain Barrier and Suppresses Appetite," Life Sciences, 58 (16): 1347-1354. CW Sim, L., et al., "In vitro Autoradiography of Receptor-Activated G Proteins in Rat Brain by Agonist-stimulated Guanylyl 5'-[γ[³⁵ S]thio]-Triphosphate Binding," Proc. Natl. Acad. Sci., USA, 1995, 92: 7242-7246. CX Terasaki, T., et al., "Oligopeptide Drug Delivery to the Brain," Amer. Chem. Soc. 1995: 297-316. CY Tsuzuki, N., et al., "Rabid Communication. Adamantane as a Brain-Directed Drug Carrier for Poorly Absorbed Drug: Antinociceptive Effects of [D-Ala*] Leu-Enkephalin Derivatives Conjugated with the 1-Adamantane Moiety," Biochemical Pharmacology, 1991, 41 (4): R5-R8. CZ Wagner, J., et al., "Neuropharmacology of Endogenous Opioid Peptides," Psychopharmacology: The Fourth Generation of Progress, 1995: 519-529. DA Weber, S.J., et al., "Neuropharmacology of Endogenous Opioid Peptides," Psychopharmacology: The Fourth Generation of Progress, 1995: 519-529. DA Weber, S.J., et al., "Whole Body and Brain Distribution of 1³H]Cyclic [D-PEN²] Enkephalin and Two Halogenated Analogs after Intravenous Administration," J. Pharm. Exper. Ther., 1991, 259: 1109-1112. Continue on Page Examiner		CQ	Ratner, R. E. et al., "Persistent	Cutaneous Insulin Allergy Resulting fro	om High-Molecular Weight Insulin	
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CS Saffran, M. et al., "A New Approach to the Oral Administration of Insulin and Other Peptide Drugs," Science, 1986, 233: 1081-1084. CT Sakaeda, T., et al., "Conjugation with L-Glutamic Acid for Brain Drug Delivery," Proceed. Intern. Symp. Control. Rel. Bioact. Mater., 1966, 23: 607-608. CU Shashoua V.E., et al., "γ-Aminobutyric Acid Esters. 1. Synthesis, Brain Uptake, and Pharmacological Studies of Aliphatic and Steroid Esters of γ-Aminobutyric Acid," J. Med. Chem., 1984, 27 (5): 660-664. CV Shashoua, V.E., et al., "N-Docosahexaenoyl, 3 Hydroxytyramine: A Dopaminergic Compound that Penetrates the Blood-Brain Barrier and Suppresses Appetite," Life Sciences, 58 (16): 1347-1354. CW Sim, L., et al., "In vitro Autoradiography of Receptor-Activated G Proteins in Rat Brain by Agonist-stimulated Guanylyl 5'-[γ[³⁵ S]thio]-Triphosphate Binding," Proc. Natl. Acad. Sci., USA, 1995, 92: 7242-7246. CX Terasaki, T., et al., "Oligopeptide Drug Delivery to the Brain," Amer. Chem. Soc. 1995: 297-316. CY Tsuzuki, N., et al., "Rabid Communication. Adamantane as a Brain-Directed Drug Carrier for Poorly Absorbed Drug: Antinociceptive Effects of [D-Ala²] Leu-Enkephalin Derivatives Conjugated with the 1-Adamantane Moiety," Biochemical Pharmacology, 1991, 41 (4): R5-R8. CZ Wagner, J., et al., "Neuropharmacology of Endogenous Opioid Peptides," Psychopharmacology: The Fourth Generation of Progress, 1995: 519-529. DA Weber, S.J., et al., "Distribution and Analgesia of [³H][D-PEN², D-PEN³] Enkephalin and Two Halogenated Analogs after Intravenous Administration," J. Pharm. Exper. Ther., 1991, 259: 1109-1112. DB Weber, S.J., et al., "Whole Body and Brain Distribution of [³H]Cyclic [D-PEN², D-PEN³] Enkephalin after Intraperitoneal, Intravenous, Oral and Subcutaneous Administration," J. Pharm. Exper. Ther., 1992, 263: 1308-1316.		CR			Blood of Insulin-Using Diabetic	
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CT Sakaeda, T., et al., "Conjugation with L-Glutamic Acid for Brain Drug Delivery," Proceed. Intern. Symp. Control. Rel. Bioact. Mater., 1966, 23: 607-608. CU Shashoua V.E., et al., "γ-Aminobutyric Acid Esters. 1. Synthesis, Brain Uptake, and Pharmacological Studies of Aliphatic and Steroid Esters of γ-Aminobutyric Acid," 1. Med. Chem., 1984, 27 (5): 660-664. CV Shashoua, V.E., et al., "N-Docosahexaenoyl, 3 Hydroxytyramine: A Dopaminergic Compound that Penetrates the Blood-Brain Barrier and Suppresses Appetite," Life Sciences, 58 (16): 1347-1354. CW Sim, L., et al., "In vitro Autoradiography of Receptor-Activated G Proteins in Rat Brain by Agonist-stimulated Guanylyl 5'-[γ[3*5]thio]-Triphosphate Binding," Proc. Natl. Acad. Sci., USA, 1995, 92: 7242-7246. CX Terasaki, T., et al., "Oligopeptide Drug Delivery to the Brain," Amer. Chem. Soc. 1995: 297-316. CY Tsuzuki, N., et al., "Rabid Communication. Adamantane as a Brain-Directed Drug Carrier for Poorly Absorbed Drug: Antinociceptive Effects of [D-Ala²] Leu-Enkephalin Derivatives Conjugated with the 1-Adamantane Moiety," Biochemical Pharmacology, 1991, 41 (4): R5-R8. CZ Wagner, J., et al., "Neuropharmacology of Endogenous Opioid Peptides," Psychopharmacology: The Fourth Generation of Progress, 1995: 519-529. DA Weber, S.J., et al., "Distribution and Analgesia of [³H][D-PEN², D-PEN³] Enkephalin and Two Halogenated Analogs after Intravenous Administration," J. Pharm. Exper. Ther., 1991, 259: 1109-1112. DB Weber, S.J., et al., "Whole Body and Brain Distribution of [³H](Cyclic [D-PEN², D-PEN³] Enkephalin after Intraperitoneal, Intravenous, Oral and Subcutaneous Administration," J. Pharm. Exper. Ther., 1992, 263: 1308-1316. Continue on Page Examiner		CS	Saffran, M. et al., "A New App	roach to the Oral Administration of this	unn and Other Peptide Drugs,	
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Studies of Aliphatic and Steroid Esters of γ-Aminobutyric Acid," J. Med. Chem., 1984, 27 (5): 660-664. CV Shashoua, V.E., et al., "N-Docosahexaenoyl, 3 Hydroxytyramine: A Dopaminergic Compound that Penetrates the Blood-Brain Barrier and Suppresses Appetite," Life Sciences, 58 (16): 1347-1354. CW Sim, L., et al., "In vitro Autoradiography of Receptor-Activated G Proteins in Rat Brain by Agonist-stimulated Guanylyl 5'-[γ[35]Slthio]-Triphosphate Binding," Proc. Natl. Acad. Sci., USA, 1995, 92: 7242-7246. CX Terasaki, T., et al., "Oligopeptide Drug Delivery to the Brain," Amer. Chem. Soc. 1995: 297-316. CY Tsuzuki, N., et al., "Rabid Communication. Adamantane as a Brain-Directed Drug Carrier for Poorly Absorbed Drug: Antinociceptive Effects of [D-Ala²] Leu-Enkephalin Derivatives Conjugated with the 1-Adamantane Moiety," Biochemical Pharmacology, 1991, 41 (4): R5-R8. CZ Wagner, J., et al., "Neuropharmacology of Endogenous Opioid Peptides," Psychopharmacology: The Fourth Generation of Progress, 1995: 519-529. DA Weber, S.J., et al., "Distribution and Analgesia of [³H][D-PEN², D-PEN³] Enkephalin and Two Halogenated Analogs after Intravenous Administration," J. Pharm. Exper. Ther., 1991, 259: 1109-1112. DB Weber, S.J., et al., "Whole Body and Brain Distribution of [³H]Cyclic [D-PEN², D-PEN³] Enkephalin after Intraperitoneal, Intravenous, Oral and Subcutaneous Administration," J. Pharm. Exper. Ther., 1992, 263: 1308-1316. Continue on Page Examiner		CU	Shashoua V.E., et al., "y-Amino	butyric Acid Esters. 1. Synthesis, Brai	n Uptake, and Pharmacological	
Penetrates the Blood-Brain Barrier and Suppresses Appetite," Life Sciences, 58 (16): 1347-1354. CW Sim, L., et al., "In vitro Autoradiography of Receptor-Activated G Proteins in Rat Brain by Agonist-stimulated Guanylyl 5'-[\gamma_1^{15}S]thio]-Triphosphate Binding," Proc. Natl. Acad. Sci., USA, 1995, 92: 7242-7246. CX Terasaki, T., et al., "Oligopeptide Drug Delivery to the Brain," Amer. Chem. Soc. 1995: 297-316. CY Tsuzuki, N., et al., "Rabid Communication. Adamantane as a Brain-Directed Drug Carrier for Poorly Absorbed Drug: Antinociceptive Effects of [D-Ala²] Leu-Enkephalin Derivatives Conjugated with the 1-Adamantane Moiety," Biochemical Pharmacology, 1991, 41 (4): R5-R8. CZ Wagner, J., et al., "Neuropharmacology of Endogenous Opioid Peptides," Psychopharmacology: The Fourth Generation of Progress, 1995: 519-529. DA Weber, S.J., et al., "Distribution and Analgesia of [³H][D-PEN², D-PEN⁵] Enkephalin and Two Halogenated Analogs after Intravenous Administration," J. Pharm. Exper. Ther., 1991, 259: 1109-1112. DB Weber, S.J., et al., "Whole Body and Brain Distribution of [³H]Cyclic [D-PEN², D-PEN⁵] Enkephalin after Intraperitoneal, Intravenous, Oral and Subcutaneous Administration," J. Pharm. Exper. Ther., 1992, 263: 1308-1316. Continue on Page Examiner			Studies of Aliphatic and Steroic	d Esters of γ-Aminobutyric Acid," J. M.	ed. Chem., 1984, 27 (5): 660-664.	
CW Sim, L., et al., "In vitro Autoradiography of Receptor-Activated G Proteins in Rat Brain by Agonist-stimulated Guanylyl 5'-[y[3 ³ S]thio]-Triphosphate Binding," Proc. Natl. Acad. Sci., USA, 1995, 92: 7242-7246. CX Terasaki, T., et al., "Oligopeptide Drug Delivery to the Brain," Amer. Chem. Soc. 1995: 297-316. CY Tsuzuki, N., et al., "Rabid Communication. Adamantane as a Brain-Directed Drug Carrier for Poorly Absorbed Drug: Antinociceptive Effects of [D-Ala ²] Leu-Enkephalin Derivatives Conjugated with the 1-Adamantane Moiety," Biochemical Pharmacology, 1991, 41 (4): R5-R8. CZ Wagner, J., et al., "Neuropharmacology of Endogenous Opioid Peptides," Psychopharmacology: The Fourth Generation of Progress, 1995: 519-529. DA Weber, S.J., et al., "Distribution and Analgesia of [3H][D-PEN ² , D-PEN ⁵] Enkephalin and Two Halogenated Analogs after Intravenous Administration," J. Pharm. Exper. Ther., 1991, 259: 1109-1112. DB Weber, S.J., et al., "Whole Body and Brain Distribution of [3H]Cyclic [D-PEN ² , D-PEN ⁵] Enkephalin after Intraperitoneal, Intravenous, Oral and Subcutaneous Administration," J. Pharm. Exper. Ther., 1992, 263: 1308-1316. Continue on Page Examiner		CV	Shashoua, V.E., et al., "N-Doco	osahexaenoyl, 3 Hydroxytyramine: A D	opaminergic Compound that	
stimulated Guanylyl 5'-[y[³⁵ S]thio]-Triphosphate Binding," Proc. Natl. Acad. Sci., USA, 1995, 92: 7242-7246. CX Terasaki, T., et al., "Oligopeptide Drug Delivery to the Brain," Amer. Chem. Soc. 1995: 297-316. CY Tsuzuki, N., et al., "Rabid Communication. Adamantane as a Brain-Directed Drug Carrier for Poorly Absorbed Drug: Antinociceptive Effects of [D-Ala²] Leu-Enkephalin Derivatives Conjugated with the 1-Adamantane Moiety," Biochemical Pharmacology, 1991, 41 (4): R5-R8. CZ Wagner, J., et al., "Neuropharmacology of Endogenous Opioid Peptides," Psychopharmacology: The Fourth Generation of Progress, 1995: 519-529. DA Weber, S.J., et al., "Distribution and Analgesia of [³H][D-PEN², D-PEN⁵] Enkephalin and Two Halogenated Analogs after Intravenous Administration," J. Pharm. Exper. Ther., 1991, 259: 1109-1112. DB Weber, S.J., et al., "Whole Body and Brain Distribution of [³H]Cyclic [D-PEN², D-PEN⁵] Enkephalin after Intraperitoneal, Intravenous, Oral and Subcutaneous Administration," J. Pharm. Exper. Ther., 1992, 263: 1308-1316. Continue on Page Examiner DATE CONSIDERED			Penetrates the Blood-Brain Bar	rier and Suppresses Appetite," Life Sci	ences, 58 (10): 1347-1334.	
T246. CX Terasaki, T., et al., "Oligopeptide Drug Delivery to the Brain," Amer. Chem. Soc. 1995: 297-316. CY Tsuzuki, N., et al., "Rabid Communication. Adamantane as a Brain-Directed Drug Carrier for Poorly Absorbed Drug: Antinociceptive Effects of [D-Ala²] Leu-Enkephalin Derivatives Conjugated with the 1-Adamantane Moiety," Biochemical Pharmacology, 1991, 41 (4): R5-R8. CZ Wagner, J., et al., "Neuropharmacology of Endogenous Opioid Peptides," Psychopharmacology: The Fourth Generation of Progress, 1995: 519-529. DA Weber, S.J., et al., "Distribution and Analgesia of [³H][D-PEN², D-PEN⁵] Enkephalin and Two Halogenated Analogs after Intravenous Administration," J. Pharm. Exper. Ther., 1991, 259: 1109-1112. DB Weber, S.J., et al., "Whole Body and Brain Distribution of [³H]Cyclic [D-PEN², D-PEN⁵] Enkephalin after Intraperitoneal, Intravenous, Oral and Subcutaneous Administration," J. Pharm. Exper. Ther., 1992, 263: 1308-1316. Continue on Page Examiner DATE CONSIDERED		cw	Sim, L., et al., "In vitro Autorac	diography of Receptor-Activated G Pro	A and Soi LISA 1005 02: 7242	
CX Terasaki, T., et al., "Oligopeptide Drug Delivery to the Brain," Amer. Chem. Soc. 1995: 297-316. CY Tsuzuki, N., et al., "Rabid Communication. Adamantane as a Brain-Directed Drug Carrier for Poorly Absorbed Drug: Antinociceptive Effects of [D-Ala²] Leu-Enkephalin Derivatives Conjugated with the 1-Adamantane Moiety," Biochemical Pharmacology, 1991, 41 (4): R5-R8. CZ Wagner, J., et al., "Neuropharmacology of Endogenous Opioid Peptides," Psychopharmacology: The Fourth Generation of Progress, 1995: 519-529. DA Weber, S.J., et al., "Distribution and Analgesia of [³H][D-PEN², D-PEN⁵] Enkephalin and Two Halogenated Analogs after Intravenous Administration," J. Pharm. Exper. Ther., 1991, 259: 1109-1112. DB Weber, S.J., et al., "Whole Body and Brain Distribution of [³H]Cyclic [D-PEN², D-PEN⁵] Enkephalin after Intraperitoneal, Intravenous, Oral and Subcutaneous Administration," J. Pharm. Exper. Ther., 1992, 263: 1308-1316. Continue on Page Examiner DATE CONSIDERED			•	nioj-Tripnosphate Binding, Proc. Nati	. Acad. Sci., USA, 1993, 92. 7242-	
CY Tsuzuki, N., et al., "Rabid Communication. Adamantane as a Brain-Directed Drug Carrier for Poorly Absorbed Drug: Antinociceptive Effects of [D-Ala²] Leu-Enkephalin Derivatives Conjugated with the 1-Adamantane Moiety," Biochemical Pharmacology, 1991, 41 (4): R5-R8. CZ Wagner, J., et al., "Neuropharmacology of Endogenous Opioid Peptides," Psychopharmacology: The Fourth Generation of Progress, 1995: 519-529. DA Weber, S.J., et al., "Distribution and Analgesia of [³H][D-PEN², D-PEN⁵] Enkephalin and Two Halogenated Analogs after Intravenous Administration," J. Pharm. Exper. Ther., 1991, 259: 1109-1112. DB Weber, S.J., et al., "Whole Body and Brain Distribution of [³H]Cyclic [D-PEN², D-PEN⁵] Enkephalin after Intraperitoneal, Intravenous, Oral and Subcutaneous Administration," J. Pharm. Exper. Ther., 1992, 263: 1308-1316. Continue on Page Examiner DATE CONSIDERED		CX		de Drug Delivery to the Brain," Amer.	Chem. Soc. 1995: 297-316.	
Absorbed Drug: Antinociceptive Effects of [D-Ala²] Leu-Enkephalin Derivatives Conjugated with the 1- Adamantane Moiety," Biochemical Pharmacology, 1991, 41 (4): R5-R8. CZ Wagner, J., et al., "Neuropharmacology of Endogenous Opioid Peptides," Psychopharmacology: The Fourth Generation of Progress, 1995: 519-529. DA Weber, S.J., et al., "Distribution and Analgesia of [³H][D-PEN², D-PEN⁵] Enkephalin and Two Halogenated Analogs after Intravenous Administration," J. Pharm. Exper. Ther., 1991, 259: 1109-1112. DB Weber, S.J., et al., "Whole Body and Brain Distribution of [³H]Cyclic [D-PEN², D-PEN⁵] Enkephalin after Intraperitoneal, Intravenous, Oral and Subcutaneous Administration," J. Pharm. Exper. Ther., 1992, 263: 1308-1316. Continue on Page Examiner DATE CONSIDERED						
Adamantane Moiety," Biochemical Pharmacology, 1991, 41 (4): R5-R8. CZ Wagner, J., et al., "Neuropharmacology of Endogenous Opioid Peptides," Psychopharmacology: The Fourth Generation of Progress, 1995: 519-529. DA Weber, S.J., et al., "Distribution and Analgesia of [3H][D-PEN², D-PEN⁵] Enkephalin and Two Halogenated Analogs after Intravenous Administration," J. Pharm. Exper. Ther., 1991, 259: 1109-1112. DB Weber, S.J., et al., "Whole Body and Brain Distribution of [3H]Cyclic [D-PEN², D-PEN⁵] Enkephalin after Intraperitoneal, Intravenous, Oral and Subcutaneous Administration," J. Pharm. Exper. Ther., 1992, 263: 1308-1316. Continue on Page Examiner DATE CONSIDERED	Tsuzuki, N., et al., "Kabid Communication. Adamantane as a Brain-Directed Drug Carrier for Poorty Absorbed Drug: Antinocicentive Effects of ID-Ala ² l Leu-Enkenhalin Derivatives Conjugated with the 1-					
CZ Wagner, J., et al., "Neuropharmacology of Endogenous Opioid Peptides," Psychopharmacology: The Fourth Generation of Progress, 1995: 519-529. DA Weber, S.J., et al., "Distribution and Analgesia of [³H][D-PEN², D-PEN⁵] Enkephalin and Two Halogenated Analogs after Intravenous Administration," J. Pharm. Exper. Ther., 1991, 259: 1109-1112. DB Weber, S.J., et al., "Whole Body and Brain Distribution of [³H]Cyclic [D-PEN², D-PEN⁵] Enkephalin after Intraperitoneal, Intravenous, Oral and Subcutaneous Administration," J. Pharm. Exper. Ther., 1992, 263: 1308-1316. Continue on Page Examiner DATE CONSIDERED						
Fourth Generation of Progress, 1995: 519-529. DA Weber, S.J., et al., "Distribution and Analgesia of [³H][D-PEN², D-PEN⁵] Enkephalin and Two Halogenated Analogs after Intravenous Administration," J. Pharm. Exper. Ther., 1991, 259: 1109-1112. DB Weber, S.J., et al., "Whole Body and Brain Distribution of [³H]Cyclic [D-PEN², D-PEN⁵] Enkephalin after Intraperitoneal, Intravenous, Oral and Subcutaneous Administration," J. Pharm. Exper. Ther., 1992, 263: 1308-1316. Continue on Page Examiner DATE CONSIDERED	Adamantane Wolety, Biochemical Finantiacology, 1991, 41 (4). Ros No.					
DA Weber, S.J., et al., "Distribution and Analgesia of [³H][D-PEN², D-PEN⁵] Enkephalin and Two Halogenated Analogs after Intravenous Administration," J. Pharm. Exper. Ther., 1991, 259: 1109-1112. DB Weber, S.J., et al., "Whole Body and Brain Distribution of [³H]Cyclic [D-PEN², D-PEN⁵] Enkephalin after Intraperitoneal, Intravenous, Oral and Subcutaneous Administration," J. Pharm. Exper. Ther., 1992, 263: 1308-1316. Continue on Page Examiner DATE CONSIDERED		~~	Fourth Generation of Progress.	1995: 519-529.		
Halogenated Analogs after Intravenous Administration," J. Pharm. Exper. Ther., 1991, 259: 1109-1112. DB Weber, S.J., et al., "Whole Body and Brain Distribution of [³H]Cyclic [D-PEN², D-PEN⁵] Enkephalin after Intraperitoneal, Intravenous, Oral and Subcutaneous Administration," J. Pharm. Exper. Ther., 1992, 263: 1308-1316. Continue on Page Examiner DATE CONSIDERED		DA	Weber, S.J., et al., "Distribution	n and Analgesia of [3H][D-PEN2, D-PE	N ⁵] Enkephalin and Two	
DB Weber, S.J., et al., "Whole Body and Brain Distribution of [3H]Cyclic [D-PEN2, D-PEN3] Enkephalin after Intraperitoneal, Intravenous, Oral and Subcutaneous Administration," J. Pharm. Exper. Ther., 1992, 263: 1308-1316. Continue on Page Examiner DATE CONSIDERED			Halogenated Analogs after Intra	avenous Administration," J. Pharm. Ex	per. Ther., 1991, 259: 1109-1112.	
Intraperitoneal, Intravenous, Oral and Subcutaneous Administration," J. Pharm. Exper. Ther., 1992, 263: 1308-1316. Continue on Page Examiner DATE CONSIDERED		DB	Weber, S.J., et al., "Whole Boo	ly and Brain Distribution of [3H]Cyclic	[D-PEN ² , D-PEN ³] Enkephalin after	
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EXAMINER INITIAL		PATENT NUMBER	ISSUE DATE	NAME	CLASS	SUBCLASS	IF APPROPRIATE
	AA	4,585,754	29 Apr. 1986	Meisner et al.			
	AB	4,179,337	18 Dec. 1979	Davis et al.			
	AC	4,003,792	18 Jan. 1977	Mill et al.	 		
	AD	4,849,405	18 Jul. 1989	Ecanow			
	AE	5,013,556	7 May 1991	Woodle et al.			
	AF	4,963,367	16 Oct. 1990	Ecanow			
	AG	4,044,196	23 Aug. 1977	Hüper et al.	1		
	AH	4,717,566	5 Jan. 1988	Eckenhoff et al.			
	AI	4,698,264	6 Oct. 1987	Steinke	1		
	AJ	4,684,524	4 Aug. 1987	Eckenhoff et al.			
	AK	4,410,547	18 Oct. 1983	Ueno et al.			
	AL	3,256,153	14 Jun. 1966	Heimlich			
	AM	4,935,246	19 Jun. 1990	Ahrens			
	AN	4,797,288	10 Jan 1989	Sharma et al.			
	AO	4,744,976	17 May 1988	Snipes et al.			
	AP	5,055,304	8 Oct. 1991	Makino et al.			
	AQ	5,055,300	8 Oct. 1991	Gupta			
	AR	4,772,471	20 Sep. 1988	Vanlerberghe et al.			
	AS	5,093,198	3 Mar. 1992	Speaker et al.			
	AT	4,840,799	20 Jun. 1989	Appelgren et al.		<u> </u>	
	AU	4,622,392	11 Nov. 1986	Hong et al.			
	AV	5,653,987	5 Aug. 1997	Modi et al.	<u> </u>	DECE	\
	AW	5,792,834	11 Aug. 1998	Hakimi et al.		RECE	ļ
	AX	5,595,732	21 Jan. 1997	Hakimi et al.		טבט י.	, 1900
	AY	5,539,063	23 Jul. 1996	Hakimi et al.		Group	2700
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